REVIEW

Other antimicrobials of interest in the era of extended-spectrum β-lactamases: fosfomycin, nitrofurantoin and tigecycline

J. Garau

Department of Medicine, Hospital Mutua de Terrassa, University of Barcelona, Barcelona, Spain

ABSTRACT

The progressive increase of extended-spectrum β-lactamase (ESBL) -producing enteric bacteria in recent years has called for a re-evaluation of current antibiotic therapy for these infections. The activity and potential use of two old antimicrobials, nitrofurantoin and fosfomycin, and the new compound tigecycline for treatment of infections due to ESBL-producing Enterobacteriaceae, with special emphasis on E. coli, are reviewed. Fosfomycin continues to be active against the most common uropathogens; in a recent survey from Spain, among the 428 ESBL-producing isolates, the resistance rate of *E. coli* to fosfomycin was 0.3%, whereas the resistance rate of K. pneumoniae was 7.2%. Other recent surveys, from other parts of the world, confirm the activity of fosfomycin against ESBL-producing E. coli. The rate of resistance to nitrofurantoin in recent surveys in the USA and Canada was 1.1% among 1142 isolates of E. coli from outpatient urinary isolates. However, among 115 clinical isolates of *E. coli* ESBL producers, only 71.3% were sensitive to nitrofurantoin. Also, *E. coli* resistance to nitrofurantoin has been reported to be high in a recent survey in Latin American hospitals and in Italy. Tigecycline is a glycylcycline that circumvents efflux and ribosomal protection, the two most frequent genetic mechanisms of tetracycline resistance. The recent activity of tigecycline against 285 nonclonally related isolates expressing well-characterised ESBLs from hospital settings and the community reveal susceptibility rates for tigecycline of 97.5%. Because responses to nitrofurantoin may be less satisfactory and may require longer courses of therapy, nitrofurantoin is considered to be an alternative, rather than a first-line, therapeutic agent for this clinical syndrome. Fosfomycin trometamol is a safe and effective alternative for the treatment of cystitis and asymptomatic UTI during pregnancy, and has become, in many countries, the first choice for treatment of any type of cystitis. Finally, for treatment of systemic infections in the hospital setting, tigecycline could be an option that would reduce selection for ESBL-producing organisms.

Keywords ESBL, *Escherichia coli*, fosfomycin, nitrofurantoin, review, tigecycline, urinary tract infection

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INTRODUCTION

The progressive increase of extended-spectrum β-lactamase (ESBL) -producing enteric bacteria in recent years has generated the need to re-evaluate current antibiotic therapy for these infections. The matter is increasingly important today in countries where the prevalence of ESBL-producing *Escherichia coli* has increased considerably at the community level, fuelled by the emergence and dissemination of CTX-M enzymes in this species in many parts of the world [1]. The burden of disease due to *E. coli* infections is enormous. In the elderly population, the incidence of community-onset *E. coli* bacteraemia was 150 cases/100 000 person-years, which is approximately three times higher than the rate of pneumococcal bacteraemia in this population. It is also substantially higher than the rates of community-onset bacteraemia due to *Staphylococcus aureus*, group A streptococci and group B streptococci in persons ≥65 years of age, as estimated from surveillance studies of other populations. These comparisons suggest that *E. coli* is the most common cause of community-onset bacteraemia in the elderly population [2].

Corresponding author and reprint requests: J. Garau, Department of Medicine, Hospital Mutua de Terrassa, University of Barcelona, Plaza Dr Robert 5, 08221 Terrassa, Barcelona, Spain
E-mail: jgarau@garmar.e.telefonica.net

The prevalence of CTX-M types has increased dramatically since 1995 in many parts of the world. All confer resistance to amino- and ureidopenicillins, oxyimino-cephalosporins and monobactams, but not to 7-α-substituted β-lactams. The ESBL strains are increasingly associated with resistance to other non-related antimicrobials and pose significant therapeutic challenges. This associated resistance to other classes of antimicrobials is especially problematic in urinary isolates and underscores the therapeutic challenge that they represent.

In this article, the activity and potential use of two old antimicrobials, nitrofurantoin and fosfomycin, and the new compound tigecycline in infections due to ESBL-producing Enterobacteriaceae, with special emphasis on *E. coli*, are reviewed.

FOSFOMYCIN

Fosfomycin is a bactericidal antibiotic that acts as a cell-wall inhibitor by interfering with the first step in peptidoglycan biosynthesis. It has a broad spectrum of activity, with a wide therapeutic range and characteristic pharmacological properties. It penetrates excellently into various tissues [3] and cerebrospinal fluid [4], and, in Europe, is frequently administered in combination with other antimicrobial agents to combat severe bacterial infections. It exerts bactericidal activity under anaerobic conditions [5], as is the case within encapsulated purulent lesions, and has negligible protein-binding activity.

Resistance to fosfomycin develops rapidly in *E. coli* under experimental conditions, but in spite of the relatively high mutation rate *in vitro*, resistance in clinical isolates is rare. In-vitro-selected mutants show a decreased growth rate in both the absence and presence of fosfomycin; this provides an explanation for why most of the resistant bacteria have difficulty in becoming established in the bladder, due to their lowered fitness [6]. Also, many strains of *E. coli* can adhere to the bladder epithelium, and, as a result, they can be maintained in the bladder even though their growth rate is below the threshold required to prevent wash-out. Thus, if the antibiotic also decreases adhesion, this might further prevent bacterial establishment. Indeed, it has been shown that fosfomycin decreases bacterial adhesion [7], and this effect, conceivably, could also reduce resistance development. Although the mutator phenotypes found among *E. coli* expressing CTX-M β-lactamases have an increased propensity to fosfomycin resistance [8], this resistance remains rare among *E. coli* expressing CTX-M enzymes in countries with a high use of fosfomycin in the treatment of urinary tract infections (UTIs) [9].

Fosfomycin tromethamine is a stable salt of fosfomycin that is licensed for the single-dose treatment of acute uncomplicated UTIs caused by susceptible organisms. In-vitro time-kill kinetics of fosfomycin against *E. coli* and *Proteus mirabilis* show primarily concentration-dependent activity, with a prolonged post-antibiotic effect [10]. After oral administration of 3 g of the trometamine salt of fosfomycin, high urinary concentrations (1000–4000 mg/L) are achieved, and concentrations remain at 100 mg/L for at least 30–40 h, guaranteeing good efficacy in the treatment of uncomplicated UTI even after a single administration [11].

After many years of fosfomycin use, fosfomycin continues to be active against the most common uropathogens, and there is a very low incidence of resistant strains in *E. coli* (*c.* 2%). It is becoming increasingly common to isolate ESBL-producing *E. coli* from outpatients with uncomplicated UTIs. It is common to find that the same plasmid coding for ESBL also contains genes conferring resistance to several groups of antimicrobial agents, such as aminoglycosides and co-trimoxazole. The concurrence of quinolone resistance, particularly in ESBL-producing *Klebsiella pneumoniae*, is frequent, there being few alternatives for the appropriate oral treatment of uncomplicated UTIs caused by ESBL-producing microorganisms.

In a recent survey done in Spain, among the 428 ESBL-producing isolates studied, 417 (97.4%) were susceptible to fosfomycin (MIC ≤64 mg/L). The resistance rate of *E. coli* to fosfomycin was 0.3%, whereas the resistance rate of *K. pneumoniae* was 7.2%. Co-trimoxazole and ciprofloxacin were the least active antibiotic agents against ESBL-producing isolates (sensitivity <50%). Only one strain of *E. coli*, among all 290 tested, showed intermediate susceptibility to fosfomycin (MIC 128 mg/L). *K. pneumoniae* isolates had the highest MICs for fosfomycin (MIC_{50} and MIC_{90} of 16–64 mg/L) but are still within the susceptible range, whereas more than 90% of *E. coli* isolates showed very low MICs (≤4 mg/L) [9]. These results are similar to those described in previous

reports of non-ESBL-producing isolates, confirming that fosfomycin retains its activity against ESBL-producing isolates, and that cross-resistance with other classes of antimicrobial agent is not a problem at present. Also, there were no differences in fosfomycin activity against strains expressing different types of ESBL [9]. Other recent surveys in other parts of the world confirm the activity of fosfomycin against ESBL-producing *E. coli*. Thus, among 307 *E. coli* isolates collected from urine and blood from patients at a Korean tertiary-care hospital, all but one isolate was susceptible to fosfomycin (MIC_{90}) 16 mg/L), regardless of the sources of the isolates, ciprofloxacin resistance, and ESBL production [12].

NITROFURANTOIN

Nitrofurantoin is a synthetic nitrofuran antimicrobial agent that has been used for more than 50 years. It still has a role and continues to be prescribed, particularly in the ambulatory setting for uncomplicated UTIs, especially in its macro-crystalline formulation, macrodantin. The mechanism of action of nitrofurantoin is not well-understood, but activity appears to require enzymatic reduction within the bacterial cell [13]. The reduced derivatives appear to be capable of binding to ribosomal proteins. Antibacterial activity has also been shown under conditions in which nitroreductase activity was inhibited, suggesting that nitrofurantoin may act, in part, without reduction to active metabolites [13]. Susceptibility breakpoints are based on urinary concentrations of nitrofurantoin and have been correlated with eradication of bacteriuria in patients with UTIs. Strains with MIC ≤32 mg/L are considered to be sensitive. On the basis of this criterion, >90% of clinical strains of *E. coli* and *Citrobacter* spp. are sensitive. In contrast, only a minority of strains of *Enterobacter* spp. (20%) and *Klebsiella* spp. (45%) are susceptible, and members of the genera *Proteus*, *Providencia*, *Morganella*, *Serratia*, *Acinetobacter* and *Pseudomonas* are almost always resistant [13].

Resistant strains of *E. coli*, with chromosomal or plasmid-mediated resistance, have been associated with inhibition of nitrofuran reductase activity, thereby decreasing the production of the active derivative. However, the emergence of nitrofurantoin-resistant variants from initially susceptible pathogens has been rare, despite many years of clinical use.

The rate of resistance to nitrofurantoin in recent surveys in the USA and Canada was 1.1% among 1142 isolates of *E. coli* from outpatient urinary isolates [14]. Very similar results were found in France; 1.8% of all urinary *E. coli* isolates were sensitive to nitrofurantoin in 2005 [15]. However, among 115 clinical isolates of *E. coli* ESBL producers, only 71.3% were sensitive to nitrofurantoin [16]. Also, *E. coli* resistance to nitrofurantoin has been reported to be high in a recent survey in Latin American hospitals (13%) [17] and in Italy (20%) [18]. In *K. pneumoniae*, the ESBL producers had significantly diminished susceptibility, as compared with a non-ESBL producer, to nitrofurantoin ($p < 0.001$) [19].

Absorption of oral nitrofurantoin is 40–50%, and this is enhanced when it is taken with food; serum concentrations are low to undetectable, and urine concentrations are 50–250 mg/L. It should not be used in patients with renal failure.

TIGECYCLINE

Tigecycline is a glycylcycline derivative of minocycline with in-vitro bacteriostatic activity. It has a broad antibacterial spectrum, including Gram-positive, Gram-negative, atypical and anaerobic bacteria [20,21]. Tigecycline circumvents efflux and ribosomal protection, the two most frequent genetic mechanisms of tetracycline resistance, and has MICs <2 mg/L for Enterobacteriaceae except proteae [21,22]. It is also unaffected by the presence of co-resistance to unrelated antimicrobials, such as β-lactams, aminoglycosides and quinolones.

The activities of tigecycline against 285 non-clonally related isolates (172 from *E. coli*, 84 from *Klebsiella* spp., 20 from *Enterobacter* spp., five from *Salmonella* spp., and four from *Citrobacter* spp.) expressing well-characterised ESBLs from hospital and the community area of influence have been recently reported from Madrid, Spain. Susceptibility rates for tigecycline were 97.5%; tigecycline (mode MIC 0.5 mg/L; MIC_{90} 1 mg/L) was four- to 256-fold more active than doxycycline and minocycline (mode MIC range 2–128 mg/L). CTX-Ms were the most frequent ESBLs (61.4%), 65.8% in community isolates and 58.6% in nosocomial isolates. SHV and TEM variants constituted 22.8% and 15.8% of the ESBLs, respectively.

Overall co-resistance rates were as follows: gentamicin, 27.4%; tobramycin, 27.4%; amikacin,

6.7%. Resistance levels of sulfonamide (61.7%), trimethoprim (52.3%) and ciprofloxacin (37.2%) were significantly ($p < 0.001$) associated with CTX-M-9 producers. No tigecycline resistance was observed, although seven *K. pneumoniae* isolates exhibited intermediate MICs (4 mg/L) [23].

Among a collection of 846 ESBL-producing and AmpC-hyperproducing Enterobacteriaceae from the UK, 703 (83%) were susceptible at the EUCAST breakpoint of ≤1 mg/L; 108 (12.7%) were intermediate, with MICs of 2 mg/L, and 35 (4.1%) were resistant, with MICs of >2 mg/L. In the case of *E. coli*, 99% (417/420) of the tigecycline MICs fell between 0.125 and 1 mg/L, and only three isolates, all hyperproducers of AmpC, were intermediate, with none being resistant [24].

CONCLUSION

The emergence of ESBL-producing *E. coli* limits the therapeutic options considerably. Not only are most β-lactams no longer active, but the associated co-resistance reduces the options even further. In this scenario, alternative antimicrobial compounds are needed to cover infections in which these isolates are increasingly involved.

In the outpatient setting, high resistance rates for β-lactams, co-trimoxazole and fluoroquinolones restrict empirical antibiotic use. The efficacy of amoxicillin–clavulanate in the treatment of ESBL-producing *E. coli* strains that are sensitive to this combination has not been well-established; although, in the case of *E. coli* UTI, it can cure the infection, the current prevalence of resistance to amoxicillin–clavulanate in *E. coli* of 10% or more in some parts of the world limits considerably its therapeutic use for this indication. For this reason, nitrofurantoin and fosfomycin became reasonable alternatives for the treatment of uncomplicated UTIs.

Nitrofurantoin is restricted to treatment or prevention of uncomplicated cystitis; among its indications are the treatment of UTI during pregnancy when clearly indicated, but it should not be used at term.

Because responses to this agent and infections caused by susceptible pathogens may be less satisfactory and require longer courses of therapy, nitrofurantoin is considered to be an alternative rather than a first-line therapeutic agent for this clinical syndrome. On the other hand, the use of nitrofurantoin is unlikely to lead to cross-resistance to those antimicrobials that are used to treat other important infections.

Fosfomycin trometamol is a safe and effective alternative in the treatment of cystitis and of asymptomatic UTI in pregnancy. Recently, its use has increased dramatically in certain countries, and it has become the first choice for any type of cystitis [25].

In systemic infections in the hospital setting, tigecycline, in the absence of cross-resistance with other compounds, could represent an opportunity to reduce the intensity of selection for ESBL-producing organisms derived from the use of other antimicrobial agents. Co-resistance, such as that found in a significant proportion of ESBL-producing isolates, precludes the empirical use of most of the antimicrobial families, particularly in the case of severe infections. The efficacy of the combination of a β-lactam and a β-lactamase inhibitor is unclear, as treatment failures have been reported. Carbapenems represent the first option when these infections are caused by ESBL producers, although this option is jeopardised by the presence of strains producing metallo-β-lactamases. In-vitro data support the assumption that tigecycline can also be considered an alternative for infections involving multiresistant ESBL-producing isolates. In the case of UTI, it remains to be seen whether the low concentrations of tigecycline attained in the urine are sufficient to eradicate the infection caused by strains of *Klebsiella* and *Enterobacter* with intermediate resistance to the compound [24].

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